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Letter to the Editor

How Many X-Linked Genes for Non-Specific Mental Retardation (MRX) Are There?

To the Editor:

X-linked mental retardation (XLMR) is that proportion of mental retardation (MR) showing the distinctive pattern of inheritance associated with the X chromosome. XLMR is subdivided into syndromal and non-specific (MRX) forms. MRX is clinically homogeneous but genetically heterogeneous. Affected males in families segregating MRX have no consistent phenotypic expression apart from their MR to distinguish them from unaffected males or affected males in other MRX families. Syndromal MRs have additional neurological or phenotypic characteristics that define a syndrome, and most of these syndromes are rare. Within some families an affected male may show "soft" syndromal signs, but where this is not evident in other affected males from the same family, the MR is diagnosed as non-specific. Delineation from fragile X syndrome or FRAXE MR can now be confidently made with the aid of direct molecular tests which detect the $(CCG)_n$ expansion at either *FRAXA* or *FRAXE*. MRX can be expressed in carrier females but with milder manifestations. The gene in such cases could be partially dominant or result from a skewed X-inactivation pattern in neural tissue.

Genetic heterogeneity of MRX has been demonstrated by mapping studies (Fig. 1). These studies have led to a system of nomenclature for MRX based on regional localisation between markers detecting the closest flanking recombinants [Mulley et al., 1992]. Linkage to the X chromosome is established on the basis of the significance level determined by a two-point or multipoint lod score of at least +2 [Ott, 1991]; however, exclusion from the remainder of the chromosome is desirable to eliminate the possibility of significant linkage to two non-contiguous regions of the X chromosome. Those *MRX* genes with a lod score of +2 are assigned a consecutive *MRX* number (*MRX1, MRX2,* . . .) so that the gene segregating in each family has a distinctive label. Overlapping regional localisations may represent different *MRX* loci; however, there is potential redundancy since each overlapping *MRX* may be caused by mutations within the same gene. Nomenclature is coordinated by the Nomenclature Committee, Genome Database. Consecutive symbols are assigned in the order requested by investigators as part of the publication process. Once the family is published, each symbol is appropriately referenced on the database.

The known regional localisations for MRX families, with the evidence for linkage, are presented in Table I and in Figure 1. Flanking markers are defined by recombination events with cytogenetic locations based on Nelson et al. [1995]. These results include previously unpublished reductions to regional localisations for *MRX1, MRX10, MRX11, MRX12, MRX17,* and *MRX19* obtained as described by Gedeon et al. [1994b]. Thirty-two *MRX* numbers have been assigned and are listed in the table, with the exception of *MRX23* on which we have no information. The figure shows 32 *MRX* localisations including that for FRAXE MR.

More specific localisations for MRX genes have been suggested by breakpoints of translocations between the X chromosome and an autosome in mentally impaired girls and small deletions of the X chromosome in mentally impaired boys. The region delineated in Xp22 is proximal and closely adjacent to *XG* [Ballabio et al., 1989]. The location of XG is shown in Figure 1, and only *MRX21* overlaps this region. Another region in Xq13.1 [Van der Maarel et al., 1994] lies in the *DXS453–DXYS1* interval (Fig. 1) and is crossed by localisations for *MRX4, MRX5, MRX7, MRX8, MRX13, MRX14, MRX20, MRX22,* and *MRX26*. The same localisations, with the exception of *MRX14*, also cross another region in Xq21 which is associated with mental retardation [May et al., 1995]. This again is in the *DXS453–DXYS1* interval (Fig. 1). Genes isolated from translocation breakpoints or within deletions and which are expressed in neural tissue represent candidates for those MRX families where the genes map across these regions. Another region characterised by deletions lies in Xq28 adjacent to *FRAXE* [Gedeon et al., 1995] and contains elements of the *FMR2* gene which is associated with *FRAXE* MR [Gecz et al., 1996].

The lack of distinctive clinical criteria within the MRX group of X-linked mental retardations means that currently the only approach to differentiating between them is through non-overlapping regional localisations of the associated gene [Kerr, 1991]. Locus heterogeneity can only be detected by linkage studies that assign the gene to different parts of the chromosome. Where

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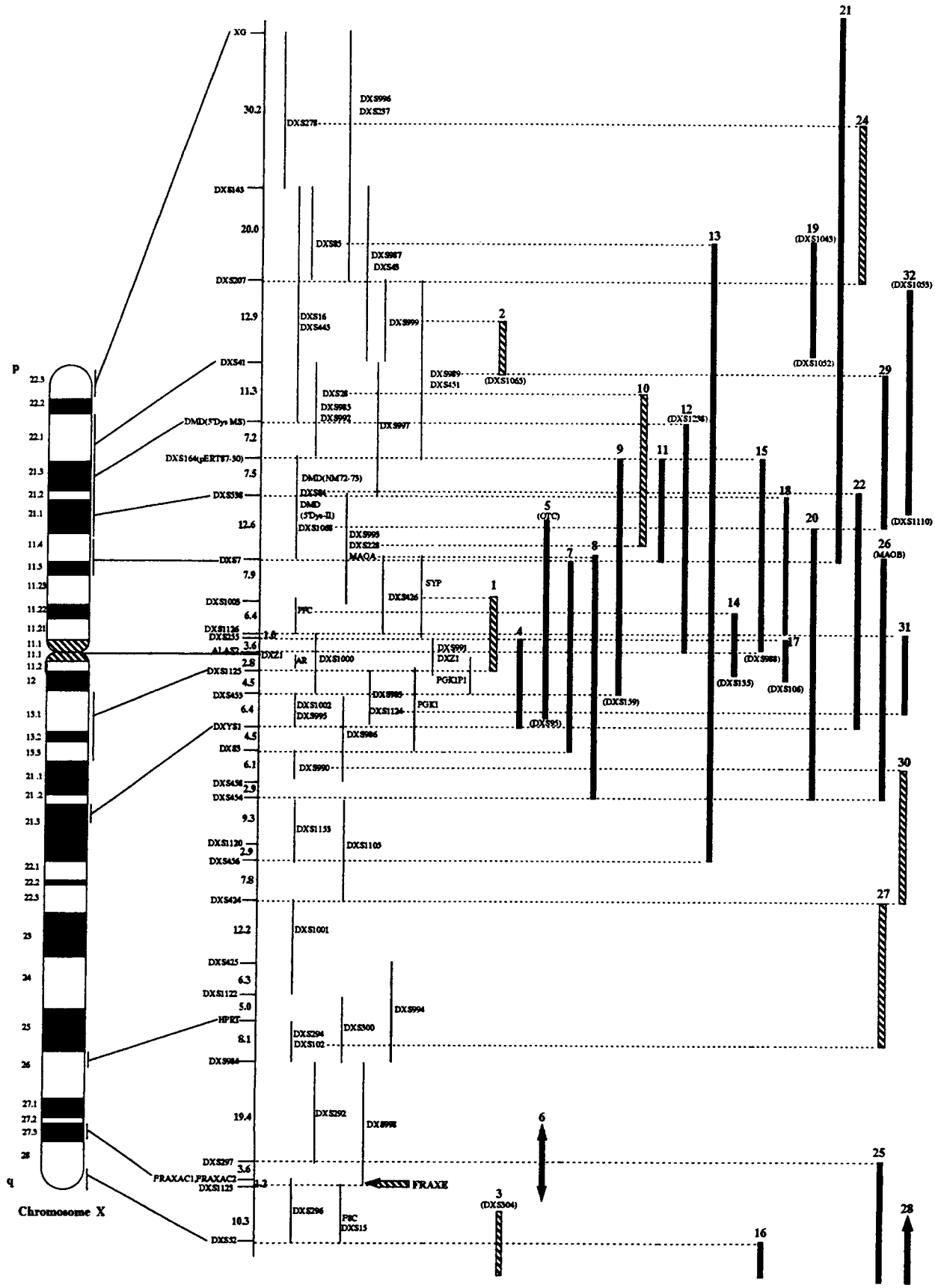

Fig. 1. Localisations for non-specific XLMR. The genetic map was modified from Donnelly et al. [1994b]. Those localisations defining the 8 distinct regions along the X chromosome are hatched. They were chosen to maximise the number of discrete regions and to give priority to the earliest MRX symbol.

TABLE I. Regional Localisations for MRX

Family	Linkage	Flanking markers		References
MRX1	z = 5.07, θ = 0.0	DXS426	DXS1125	This study[a]
	AR	p11.3	q12	
MRX2	z = 4.62, θ = 0.0	DXS999	DXS1065	Hu et al., 1994[b]
	DXS989	p22.2	p21.3	
MRX3	z = 2.89, θ = 0.0	DXS304	qter	Gedeon et al., 1991
	DXS52	Xq28		
MRX4	z = 3.38, θ = 0.0	DXS255	DXYS1	Hu et al., 1994[b]
	DXS441	p11.23	q21.31	
MRX5	z = 2.05, θ = 0.0	OTC	DXS95	Samanns et al., 1991
	DXS7	p11.4	q21.2	
MRX6	z = 2.11, θ = 0.0	Not known	Not known	Kondo et al., 1991
	DXS369			
MRX7	z = 2.44, θ = 0.0	DXS7	DXS3	Jedele et al., 1992
	DXYS1	p11.4	q21.32	
MRX8	Multipoint	MAOA	DXS454	Schwartz et al., 1992
	z = 2.36	p11.3	q21.33	
MRX9	z = 3.82, θ = 0.0	DXS164	DXS159	Willems et al., 1993
	MAOA	p21.1	q12	
MRX10	z = 4.14, θ = 0.0	DXS28	DXS228	This study[c]
	DXS1236	p21.3	p11.4	
MRX11	z = 3.86, θ = 0.0	DXS164	DXS7	This study[c]
	DXS1068	p21.1	p11.4	
MRX12	z = 3.31, θ = 0.0	DXS1238	ALAS2	This study[c]
	DYSII, DXS538, CYBB, MAOB and DXS255	p21.2	p11.21	
MRX13	z = 2.33, θ = 0.0	DXS85	DXS456	Kerr et al., 1992
	DXYS1	p22.31	q22.3	
MRX14	z = 3.31, θ = 0.0	PFC	DXS135	Gendrot et al., 1994
	DXS255	p11.3	q12	and C. Moraine (pers. commun.)
MRX15	z = 2.01, θ = 0.0	DXS164	DXS988	Moraine et al., 1994
	DXS573	p21.1	p11.22	
MRX16	z = 4.2, θ = 0.0	DXS52	qter	Moraine et al., 1994
	DXS15	q28		
MRX17	z = 2.41, θ = 0.0	DXS255	DXS106	This study[d]
	AR	p11.23	q12	
MRX18	z = 2.7, θ = 0.0	DXS538	DXS1126	Gedeon et al., 1994a
	DXS1003	p21	p11.23	
MRX19	z = 3.58, θ = 0.0	DXS1043	DXS1052	This study[e]
	DXS207, DXS987	p22.31	p22.13	
MRX20	z = 3.31, θ = 0.0	DXS1068	DXS454	Lazzarini et al., 1995
	DXS458	Xp11.4	q21.33	
MRX21	z = 2.11, θ = 0.0	pter	DXS7	Kozak et al., 1993
	DXS164, DXS278		p11.4	
MRX22	z = 3.25, θ = 0.0	DXS84	DXYS31	Passos-Bueno et al., 1993
	DXS14	p21.1	q21.31	
MRX23				Not known
MRX24	z = 2.28	DXS278	DXS207	Martinez et al., 1995
	multipoint	p22.32	p22.2	
MRX25	z = 2.52, θ = 0.0	DXS297	qter	Nordström et al., 1992
	DXS52	q27.3		
MRX26	z = 4.21, θ = 0.0	MAOB	DXS454	Robledo et al., 1996
	DXS573 and AR	p11.3	q21.33	
MRX27	z = 4.02, θ = 0.0	DXS424	DXS102	Gedeon et al., 1996
	DXS1114	q23	q26.3	
MRX28	z = 2.8, θ = 0	Not known	Not known	Holinski-Feder et al., 1995
	DXS52			
MRX29	z = 3.31, θ = 0	DXS989	DXS1068	Hane et al., 1995
	DXS1202	p22.13	p11.4	
MRX30	z = 2.78	DXS990	DXS424	Donnelly et al., 1996
	Multipoint	q21.33	q23	
MRX31	z = 3.44, θ = 0.0	DXS1126	DXS1124	Donnelly et al., 1996
	AR	p11.23	q13	
MRX32	z = 4.21, θ = 0	DXS1053	DXS1110	Hane et al., 1996
	DXS1237	p22.2	p21.1	

[a] Update of Suthers et al. [1988] and Kerr et al. [1992].
[b] Update of Arveiler et al. [1988].
[c] Update of Kerr et al. [1992].
[d] Update of Gedeon et al. [1994a].
[e] Update of Donnelly et al. [1994a].

the gene in more than one MRX family is assigned to the same chromosomal region, it cannot be determined by linkage analysis whether only a single gene is involved, just as variable clinical indicators do not necessarily exclude allelism between syndromal MRs. Disorders mapping to the same chromosomal band and suspected to be allelic might in future be substantiated by identification of mutations in the same gene. The basis for differences in phenotype or severity may then be demonstrated. Some of the MRX genes may be found to be milder allelic forms of syndromal conditions. For now, progress in gene identification will rely on gene mapping and recognition of subtle clinical and behavioural or adaptive characteristics to differentiate co-localised subtypes as specific entities. In this manner the contributions of laboratory based molecular genetic mapping are essential to clinical nosology.

Herbst and Miller [1980] suggested that between 7 and 19 loci could account for the prevalence of MRX. Gene mapping and ultimately gene identification are the only ways to accurately determine the true number since the theoretical estimates relied upon assumptions about mutation rates, zero fitness of affected males and equal fitness of carrier and non-carrier females. None of these parameters are known exactly and subsequently entities such as fragile X syndrome and Renpenning syndrome have been dissected out of this group. Thus, the expected number of MRX genes is unclear.

A lower limit to the number of MRX genes can now be firmly established by counting the number of non-overlapping genetic localisations. Currently a minimum of 7 discrete MRX genes must exist on the basis of linkage analysis defining non-overlapping regional localisations from Xpter to Xqter for *MRX24, MRX2, MRX10, MRX1, MRX30, MRX27,* and *MRX3*. The inclusion of *FRAXE* mental retardation increases the number of separate MRX entities now known to exist to at least 8. Families with major genes responsible for borderline MR at the lower end of the normal IQ range will be difficult to ascertain as their phenotype may be integrated into that of the normal population. Brunner et al. [1993a,b] describe a family where affected men may have borderline MR. Their phenotype consisted of distinctive behavioural disturbance arising from a defect in the monoamine oxidase A gene at Xp11.23-p11.4. This disorder is more appropriately classified as a metabolic disorder with MR [Neri et al., 1994] rather than as a non-specific MR.

A dense map of PCR based genetic markers along the X chromosome has now been established [Nelson et al., 1996] to resolve regional localisations for different MRX genes (Fig. 1). The limits to the resolution of these regional localisations are determined by the size of the MRX families and the distribution of crossover events in their potentially informative meioses. The early MRX localisations were suggestive of a concentration at the pericentromeric region where non-overlapping *MRX17* and *MRX18* localisations delineate the existence of at least 2 genes [Gedeon et al., 1994a]. Although later localisations show a greater spread of MRX loci along the chromosome, there remains a greater density near the centromere and a clustering near the gene rich Xq28 region has emerged. Continual refinements to regional localisation in MRX families has led to improved enumeration of the minimum number of MRX loci. The positional candidate approach to the identification of these MRX genes remains challenging given the size of the regional localisations determined by recombinants in single families and the density of candidate genes within these intervals which affect or are expressed in neural tissue.

The efficacy of cloning genes from the breakpoints of translocations between the X chromosome and an autosome in affected girls and from within X chromosome deletions of affected boys remains to be established as a means of identifying all of the genes responsible for familial MRX. However, the first of these genes has now been identified, by the isolation of coding sequences from deletions adjacent to *FRAXE* [Gecz et al., 1996].

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NOTE ADDED IN PROOF

The *MRX23* localisation is now published [Gregg et al., 1996, Hum Mol Genet 5:411–414] and *MRX35* has been added to the known MRX localisations [Gu et al., 1996, J Med Genet 33:52–55].

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